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# Analytical Solutions to the Mathematical Models on the Effect of Drug-Inhibited on Tumor Growth

G.C.E MBAH [1] D. OMALE[2] P.B. OJIH
1.Mathematics Department, University of Nigeria Nsukka
2.Mathematical Sciences Department, Kogi State University Anyigba

**Abstract**
The treatment of cancer by Chemotherapy has become a new focus in cancer research and treatment in Cancerous cases, Natural killer, $CD8^+$ and Cytotoxic lymphocytes alone cannot effectively kill cancer cells and thus the need for chemotherapy administration in this study, we propose analytical solutions to the modified Jackson, T. L. (2002), model that included chemotherapy but particularly chemotherapy on vascular tumor growth. We applied Duhamel principle and carried out couple of analysis on the solutions of the modeled equations for various treatments using the therapy. The results from the analysis portend good revelations on cancer cell management and control using chemotherapy.
**Keywords:**Tomur, malignant, chemotherapy, Duhamel, Apoptosis, Angiogenesis, Vasculature, Carcinogenesis, Perturbation

## 1.1 INTRODUCTION

Tumour is an abnormal swelling in or on any part of the body. It is one of the classical signs of inflammation in a tissue. The swelling of an inflamed area is sometimes due to the leakage from small blood vessels of clear proteins containing fluid, which accumulates between the cells. The term tumour is applied to abnormal growth of tissue, which may be benign or malignant. Cancer is the common term for all malignant tumours; it probably derives from the Latin word for crab, “cancer” presumably because cancer adheres to any part of the body that it affects in an obstinate manner like the crab. When cancer cells that invade the blood stream are transported to another location thus creating a secondary tumour or metastases, it may be difficult to treat, because treatment may damage the normal tissue.

The mathematical model derived by de Pillis et al (2002) was solved Numerically and we feel that the models can be solved rather analytically to give better result. We know that numerical solutions are approximate solutions and in cancer treatment, approximate solution could be dangerous. As such, we revisited the models with some tractable assumptions to enable us solve the equations analytically.

Recently, records from all over the world show high rise in cancer incidence. Our hospitals are witnessing new cases of cancers, at least an average of more than one every day. According to American Cancer Society estimates, cancer caused approximately 538,000 deaths in 2004 accounting for about 23% of all deaths in the United States of America alone.

The conventional methods of treating cancer (Surgery, chemotherapy, radiation, proton therapy ETC) are not helping matters because they come with their attending negative side effects, which can also lead to death of patient receiving treatment. To this ends, our aim is to analyse existing mathematical models to help us understand the interaction between the immune and cancer cells and the effects of chemotherapy on the growth rate of tumor and also to help us predict incidence of cancer on the host. This in turn can lead to better treatment and increase in survival rate and quality of life for those struggling with cancer

In this research work, we shall be considering the mathematical models on the new treatment method; the combination methods. One major question that we hope to shed light on, by modeling cancer treatments, is how immunotherapy and chemotherapy interact. We also plan to simulate our solutions to see the behaviour of our models, after series of perturbations. Although we do not have exact experimental results, we hope that the simulation of our results show reasonable behaviour

The concepts of mathematical modeling of tumour is new in the field of Applied Mathematics. However, for 15 –years now many mathematical models of tumour growth and invasion have started appearing in the research papers.

According to Sanga et al (2006), mathematical modeling and simulation are tools that can provide a robust framework for better understanding of cancer progression and response to chemotherapy. Quaranta V; Weaver A. M; cummings, TT; Anderson AR (2005), are of the view that quantitative simulation of clinically relevant cancer situation based on experimentally validated mathematical model, provides an opportunity for the researchers, and eventually the clinician, to address data and information in the context of well formulated question, and “what if” scenarios. They pointed out that cancer research has undergone changes in the past few years, producing information, both at the basic and clinical levels. However, this is no longer the issue, rather how to handle this information has become the major obstacle to progress. Initiative approaches are no longer feasible. The next big step will be to implement mathematical modeling approaches to analyse the enormous

amount of data being produced and extract useful answers, a top-down approach to biology and medicine.

Moreover, as shown in the recent paper of Novozhilove, A. S., Fiana S. Berezouskaya; Bugene V. Koonin And Georgy P. Kareu (2006), Oncolytic viruses that specifically target tumour cells are promising anti-cancer therapeutic agents. The interaction between an oncolytic virus and tumour cells is amenable to mathematics and modeling using adaptation of techniques employed previously for modeling other type of virus-cell interaction. Their model exhibits all possible outcomes of oncolytic virus infection i.e. no effect on the tumour, stabilization or reduction of the tumour load and complete elimination of the tumour. The parameter values that result in tumour elimination, which is obviously, the desired outcome are compatible with some of the available experimental data.

Ribba B., Therry Colin and Santiago Schnell (2006), have shown that Radiotherapy outcomes are usually predicted using the quadratic model. However, this model does not integrate complex cell cycle regulation growth based on the genetic and molecular features of the evolution of colorectal cancer. The model includes key genes, cellular kinetics tissue dynamics, and macroscopic tumour evolution and radio sensitivity dependence on the cell cycle phase. They investigate the role of gene-dependent cell cycle regulation in the response of tumours to therapeutic irradiation protocols. Their model provides insight into the coupling of complex biological processes, which leads to a better understanding of on cogenesis. This hopefully will lead to improved radiation therapy.

Mathematical models of cancer growth have been the subject of research activity for many years. The Gompertzian model, logistic and power functions have been used, to describe tumour growth dynamics. These formalisms have been used to investigate different therapeutic strategies such as antiogiogenic or radiation treatments.

The work by Orme, M. C. and Chaplain, M. A. J. (2003) reveal that a spherical tumour growth and invasion with regard to the parent blood vessel vascularization, may consequently lead to metastasis. Their model described the case where the invasive tumour cells growth advancing toward the parent blood vessel were unable to reach some parts of the tumour due to competition for space with tumour cells or high internal pressure which may cause blood vessels to collapse. Fisher, et al., (2004) used epidemiological data to infer that cancer incidence increases with approximately the sixth power of age. They recognize that the rate of cancer occurrence would rise with the nth power of age if transformation required n + 1 independent steps. They further suggest that, about seven cells had to be transformed independently. This would give the observed rate of change with age. However, Armitage and Doll (2002) pointed out that if transformation happens by one-step in each of several independent cells, then tumour incidence should increase with about the sixth power of carcinogen dose.

Alexey S. Matveev and Andrey V. Savkin (2005); studied cancer chemotherapy with the application of several drugs and, the influence of tumours on normal cells and optimal chemotherapy regimes. The model indicates that the presence of tumour inhibiting the growth of normal cells in the context of multi-drug therapy may complicate the protocol. They stated that optimal drug delivery strategies are separate. Some researchers in this area justify benefits from the late intensification of the chemotherapy. Other authors proceeding from biological features different from the negative influence of tumours on the patient have concluded that early intensification of therapy is optimal.

Chattler (2004) formulated a mathematical model for cancer chemotherapy treatment when a single G2/M specific killing agent was considered as the optimal control problem. Their results show that geometric properties of the model have a direct influence on the type of controls, which are optimal. Singular arcs are not optimal if linear models are used, but for more general PK–models and PD functions, S, this does not necessarily hold, but true for regions where S is strictly convex. The optimality concentration changes as S becomes concave.

Byrne, H. M., Chaplain M. A. J., Pettet, G. J. and McELWAIN D. L. S. (1999) examined angiogenesis of tumour in terms of continuous variables which yielded qualitative phenomenological result. Their model was based or rooted in the work of Balding and McElwair (1985) which was developed from a fungal growth model proposed by Edelstain (1982). Their work has the ability to predict the brush-border effect of the advancing vascular front that has been worked upon by Muthukkaruppani et al (1982)

Mathematical modeling of deterministic reaction-diffusion equations have been used to model the spatial spread of tumour both at an early stage in its growth by Sheriatt and Nowak, (1992); Ward, J. P. and King J. R. (1999) and at the later invasive stage of tumour development by Orme and Chaplain (1996); Gatenby and Gawlinski (1996); Perumpanani et al, (1996) and Anderson et al, (2000). Solutions observed in all these models appear as invading traveling waves of cancer cells.

Ferreira, and Martins (2002), Reaction diffusion model for the growth of a vascular tumor, nutrient limited mode for a vascular cancer growth including cell proliferation motility and death was presented. [12] developed mathematical models that describes the reduction in volume of vascular tumor in response to specific chemotherapeutic administration strategies. The model consists of a system of partial differential equations governing intratumoral drug concentration

## 2.0 MODEL EQUATIONS

We propose to consider the de Pillis et al (2002) and Jackson (2002) models which include immunotherapy in addition to chemotherapy for vascular tumor growth. Using their models, we study the two coupled sets of equations, the first of which models the immune and drug interactions with the tumor and

The two important models from Jackson (2002) are given as:

$$c\left[\frac{\partial d}{\partial t}+\nabla.(ud)\right]=\Delta d+\Gamma(d_B(t)-d)-\lambda_0 d-\lambda_1 F(d,n,m) \quad for\ n+m+v=1$$

*and*

$$\frac{\partial n}{\partial t}+\nabla.(un)=\sigma_n\Delta n+n(1-\mu_1 m)-\frac{\beta_1 dn}{\gamma_1+n}$$

where d is the drug and n is the tumour cells,

while the models from de Pillis et al (2002) for tumor growth, drug used, Natural killer and $CD8^+$ and the tumor signal equations are given as:

$$\frac{\partial T}{\partial t}=d_T\nabla^2 T+\lambda_T T-I_{DT}(DT)-L_C L_{CT}(C,T)-L_N I_{NT}(N,T) \quad (2.01)$$

$$\frac{\partial D}{\partial t}=d_D\nabla^2 D-\lambda_D D+\Gamma(D_b(t)-D)-U_T I_{DT}(D,T)-U_C I_{CD}(C,D)-U_N I_{ND}(N,D) \quad (2.02)$$

$$\frac{\partial N}{\partial t}+a_N\nabla.(N\nabla S)=d_N\nabla^2 N-\lambda_N N-i_N I_{NT}(N,T)-I_{ND}(N,D) \quad (2.03)$$

$$\frac{\partial C}{\partial t}+a_C\nabla.(C\nabla S)=d_c\nabla^2 C-\lambda_C C-i_c I_{cT}(C,T)-I_{CD}(C,D) \quad (2.04)$$

$$\frac{\partial S}{\partial t}=d_S\nabla^2 S-\lambda_S.S+\alpha_S TH(-B(r,t)) \quad (2.05)$$

Here H is the standard heaviside step function

## 2.2 ASSUMPTIONS

In line with the assumptions and analysis of de Pillis et al (2002) and Jackson (2002), we make the following assumptions for the model equations of vascular tumor growth.

- The tumor cells are uniformly susceptible to drug treatment and immune interactions and there is negligible necrosis in the tumor.
- All cells and drugs within the tumor undergo diffusion and conversion.
- Tumor cell grow exponentially in the absence of chemotherapy and immune response, this growth rate could be logistic.
- The chemotherapeutic drug, the NK. Cells, the $CD8^+$ cells and the circulating lymphocytes all become inactive over time at rates proportional to their population size.
- NK cells, $CD8^+$ cells and the drug can all kill tumor cells.
- The interaction with tumor cells inactivates some fraction of the NK and the $CD8^+$ cells.
- The presence of a tumor activates both NK and $CD8^+$ cells.
- A chemical signal generated by the tumor tissue attracts NK and $CD8^+$ cells.
- Circulating lymphocytes stimulate the growth of $CD8^+$ cells and NK cells and increase at some constant rate.
- The drug kills NK, $CD8^+$ and circulating lymphocytes in addition to the tumor cells. The drugs diffuse between the tumor cells.

We define the following dependents variables for use in the equations of the model:

 

| | |
|---|---|
| $T(r,t)$ | Density of tumor cells within the tumor Where $r$ is the radius of the tumour, $t$ is the time |
| $V(r,t)$ | Density of vasculature within the tumor |
| $D(r,t)$ | Concentration of drug within the tumor tissue |
| $N(r,t)$ | Density of NK cells within the tumor tissue |
| $C(r,t)$ | Density of $CD8^+$ cells |
| $S(r,t)$ | Concentration of chemical signal that attract immune cells |
| $U(r,t)$ | Local cell velocity inside the tumor |
| $P(r,t)$ | Internal pressure inside tumor |
| $D_b t$ | Concentration of drug in blood streams |
| $D_N(t)$ | Concentration of drug in normal tissue surrounding the tumor |
| $N_N(t)$ | Density of NK cells in normal tissue surrounding the tumor |
| $C_N(t)$ | Density of $CD8^+$ cells in normal tissue |
| $L(t)$ | Density of circulating lymphocytes in the blood stream |
| $L_N$ | Amount of NK cells that is removed from normal cells as a result of death by chemotherapy In the model also, we used the following parameters: |
| $di$ | Diffusion or cell motility constant for population $i$. |
| $\lambda i`$ | Natural growth or death rate for population $i$. |
| $Ui$ | Rate at which the drug is inactivated in its interaction with population's $i$. |
| $L_N, L_C$ | Rate at which NK and $CD8^+$ cells are inactivated from interaction within the tumor. |
| $a_N, a_C$ | Attraction coefficient for NK and $CD8^+$ cells in response to the tumor signal. |
| $\alpha_s$ | Rate of signal production by tumor cells. |

We Restate the de Pillis et al (2002) models for tumor growth, drug used, Natural killer and $CD8^+$ and the tumor signal equations, given as:

$$\frac{\partial T}{\partial t} = d_T \nabla^2 T + \lambda_T T - I_{DT}(DT) - L_C L_{CT}(C,T) - L_N I_{NT}(N,T) \quad (2.1)$$

$$\frac{\partial D}{\partial t} = d_D \nabla^2 D - \lambda_D D + \Gamma(D_b(t) - D) - U_T I_{DT}(D,T) - U_C I_{CD}(C,D) - U_N I_{ND}(N,D) \quad (2.2)$$

$$\frac{\partial N}{\partial t} + a_N \nabla.(N \nabla S) = d_N \nabla^2 N - \lambda_N N - i_N I_{NT}(N,T) - I_{ND}(N,D) \quad (2.3)$$

$$\frac{\partial C}{\partial t} + a_C \nabla.(C \nabla S) = d_c \nabla^2 C - \lambda_C C - i_c I_{cT}(C,T) - I_{CD}(C,D) \quad (2.4)$$

$$\frac{\partial S}{\partial t} = d_S \nabla^2 S - \lambda_S .S + \alpha_S TH(-B(r,t)) \quad (2.5)$$

where H is the standard heaviside step function

To be able to have any meaningful analytical study of these modeled equations, introduction of some modifications in the form of assumptions are necessary. The $I$ function used above represents the interaction terms between the various populations within the tumor. For example, $I_{DT}(D,T)$ represents the interaction between the drug and the tumor cells, which we expect to depend only on the local concentration D and T. It is also assumed that the interaction has the same effect on each population involved up to some scaling multiplier.

We equally assumed that each local species is subject both to diffusion and to conventions resulting from the local cell velocity. The tumor cells have some natural growth rate but are killed by the drug and the immune cells. The drug decays at some constant rate, diffuses into (or out of) the tumor from the blood stream, and is deactivated at some rate in its interactions with both the tumor cells and immune cells. Each immune cell population undergoes natural death or inactivation as well as death or inactivation resulting from its interaction with the tumor cells and the drug. In addition, it is assumed that the tumor secretes a chemical that attract the

body's immune cells and this chemical decays at some natural rate and is produced only within the tumor boundary.

From (2.1), we see that

$$\frac{\partial T}{\partial t} = d_T \nabla^2 T + \lambda_T T - I_{DT}(DT) - L_C L_{CT}(C,T) - L_N I_{NT}(N,T)$$

where

$T$ = the Tumor population

$d_T \nabla^2 T$ = Diffusion terms

$\lambda_T T$` = growth rate of tumor

$I_{DT}(D,T)$ = Death of tumor as a result of drugs

$I_C T_{CT}(C,T)$ = Tumor removed as $CD8^+$ acts on it

$L_N I_{NT}(N,T)$ = Death of tumor as NK acts on it.

We also have equation (2.2) as:

$$\frac{\partial D}{\partial t} = d_D \nabla^2 D - \lambda_D D + \Gamma(D_b(t) - D) - U_T I_{DT}(D,T) - U_C I_{CD}(C,D) - U_N I_{ND}(N,D)$$ where

$D$ = the chemotherapeutic drug

$d_D \nabla^2 D$ = Diffusion terms

$\lambda_D$ = the decay rate

$\Gamma(D_b(t) - D)$ = from vasculature

$U_T I_{DT}(D,T)$ = the number of Tumor cells that are being removed as a result of the drug

$U_C I_{CD}(C,D)$ = introduction of the $CD8^+$ as a result of the drug

$U_N I_{ND}(N,D)$ = Inactivation of the NK as the result of the drug

Equation (2.3 )and (2.4 )also are presented respectively as:

$$\frac{\partial N}{\partial t} + a_N \nabla.(N \nabla S) = d_N \nabla^2 N - \lambda_N N - i_N I_{NT}(N,T) - I_{ND}(N,D)$$

$N$ = Represents our natural killer NK

$a_N \nabla.(N \nabla S)$ = Signal gradient

$d_N \nabla^2 N$ = Diffusion of the NK

$-\lambda_N N$ = Natural death of NK

$i_N I_{NT}(N,T)$ = Is the inactivation co-efficient of NK in T

$I_{ND}(N,D)$ = Death from drug introduction of NK in the prevention of D

and

$$\frac{\partial C}{\partial t} + a_C \nabla.(C \nabla S) = d_c \nabla^2 C - \lambda_C C - i_c I_{cT}(C,T) - I_{CD}(C,D)$$

$C$ = Represents the $CD8^+$ cells

$a_C \nabla.(C \nabla S)$ = the signal gradient

$d_c \nabla^2 C$ = the diffusion within the cells of the $CD8^+$

$\lambda_C C$ = the natural death rate of the $CD8^+$

$i_C I_{CT}(C,T)$ = Inactivation factor of the $CD8^+$ in T

$I_{CD}(C,D)$ = the death from drug inactivation of $CD8^+$ in the prevention of D

### 2.2.1 INITIAL CONDITIONS

We introduce the following parameters to be used in specifying the initial conditions of the system.

$T_o$ Initial density of tumor cells

$V_o$ Initial density of vasculature

$D_o$ Initial concentration of drug in the blood stream

$N_o$ & $C_o$ Initial concentration of NK and $CD8^+$ cells in the body tissue

$L_o$ Initial concentration of circulating lymphocytes cells in the body tissue.

We suppose that initially the only populations present in the tumor itself are the tumor and the tumor vasculature.

Systematically, we suppose that initially, there is no drug and that there are specified population of NK cells, $CD8^+$ cells and circulating lymphocytes and so we have:

$$\left.\begin{aligned} T(r,o) &= T_o \\ V(r,o) &= V_o \\ D(r,o) &= 0 \\ N(r,o) &= N_o \\ C(r,o) &= C_O \end{aligned}\right\} \tag{2.6}$$

We define the tumor boundary as a level surface of some function $B(r,t)$ where:

$$B(r,t) = r - R(\theta,\phi,t) = 0 \tag{2.7}$$

The motion of a point on the boundary $B(r,t) = 0$ is then determined by

$$n_v . \frac{dr}{dt} = u \cdot n_v , \tag{2.7b}$$

where $n_v$ is an outward normal vector to the tumor boundary. This equation (2.7b) represents the equation of motion of the drug concentration within the tumour where "*u*" is the local cell velocity. We connect the temporal and spatial temporal equations through continuity conditions at the boundary. Therefore, at the boundary $B(r,t) = 0$, we have

$$D(r,t) = D_N(t), N_r(r,t) = N_N(t), C(r,t) = C_N(t) \tag{2.8}$$

We need to introduce a new set of parameters to be used in the interaction terms

$ki$ As the susceptibility of population $i$ to the drug

$\sigma i$ Is the drug saturation coefficient for population $i$

We now give appropriate definitions for the interaction function $Iij$ in the equations. Based on the analysis presented in the de Pillis et al (2002) we model the tumor immune cell interaction as product terms

$$I_{CT} = CT$$

$$I_{NT} = NT$$

For the drug's interaction with the tumor and the immune cells, in both the systemic and local area we follow the exponential model presented by de-Pillis et al (2002). We change the derivation slightly so that the kill fraction in a time interval from $t$ to $t + \Delta t$ is

$$\frac{P(t+\Delta t) - P(t)}{P(t)} = k(1 - e^{-\sigma D})\Delta t \tag{2.9}$$

where $P$ is some cell population. Rearranging and taking the limit as $\Delta t$ goes to $0$, we have:

$$\frac{dp}{dt} = \lim_{\Delta t - o} \frac{P(t+\Delta t) - P(t)}{\Delta t} = k(1 - e^{-\sigma D}) \tag{2.10}$$

Thus, we take the local drug-cell interaction terms to be:

$$\left.\begin{aligned} I_{DT} &= k_T(1-e^{-\sigma_T D})T \\ I_{ND} &= k_N(1-e^{-\sigma_N D})N \\ I_{CD} &= k_C(1-e^{-\sigma_C D})C \end{aligned}\right\} \tag{2.11}$$

We now consider this model in the case of complete spherical symmetry, so that there is no angular dependence to any of the spatially dependence variables, and now the tumor boundary is determined by $B(r,t) = r - R(t) = 0$. Then (4.1), (4.2), (4.3), (4.4) and (4.5) become :

$$\frac{T\partial}{r^2\partial r}(r^2 u) = \lambda_T T - k_T(1-e^{-\sigma_T D})T - L_C CT - L_N NT \tag{2.12}$$

$$\frac{\partial D}{\partial t} = \frac{dD}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial D}{\partial r}) - \lambda_D D + \Gamma(D_B(t) - D) - u_T K_T(1-e^{-\sigma_T D})T$$
$$-U_N K_N(1-e^{-\sigma_N D})N - U_C K_C(1-e^{-\sigma_C D})C \tag{2.13}$$

$$\frac{\partial S}{\partial t} = \frac{dS}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial S}{\partial r}) - \lambda_S S + \alpha_S H(R(t)-r)T \tag{2.14}$$

$$\frac{\partial N}{\partial t} + a_N\left\{\frac{\partial S}{\partial r}\frac{\partial N}{\partial r} + \frac{N}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial S}{\partial r}\right)\right\}$$
$$= \frac{\partial_N}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial N}{\partial r}\right) - \lambda_N N - i_N NT - K_N(1-e^{-\sigma_N D})N \tag{2.15}$$

$$\frac{\partial C}{\partial t} + a_C\left\{\frac{\partial S}{\partial r}\frac{\partial C}{\partial r} + \frac{C}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial S}{\partial r}\right)\right\}$$
$$= \frac{\partial_C}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right) - \lambda_C C - i_C CT - K_C(1-e^{-\sigma_C D})C \tag{2.16}$$

The initial boundary of the tumor is now given by $r = R_0$, and its evolution now follows

$$\frac{dR}{dr} = u\big(R(t),t\big) \tag{2.17}$$

**NON- DIMENSIONALIZATION**

We now introduce dimensionless variables and parameters as defined below

$$r = R_{0r}, \qquad t = t_0\bar{t} \qquad \frac{\partial}{\partial r} = \frac{1}{R_0}\frac{\partial}{\partial r}, \qquad t_0 = \frac{1}{\lambda t}$$

$$U = \frac{R_0}{t_0}\bar{u}, \qquad T = \frac{1}{V_C}\bar{T}, \qquad \bar{T}_0 = \frac{1}{V_C}\bar{T}_0 \tag{2.18}$$

c

$$\Gamma = \frac{1}{t_o}\bar{u}, \qquad \lambda_c = \frac{1}{t_o}\bar{\lambda}_c, \lambda_N = \frac{1}{t_o}\bar{\lambda}_N, \ \lambda_D = \frac{1}{t_o}\bar{\lambda}D, \lambda_s = \frac{1}{t_o}\bar{\lambda}_s$$

Substituting equation (2.18) into the equation (2.12) – (2.16) yields after simplification and dropping the bars for convenience, the following equations:

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u) = 1 - k_T(1-e^{-\sigma_T D})T - L_C C - L_N N \tag{2.19}$$

$$\frac{\partial D}{\partial t} = \frac{dD}{r^2}\frac{\partial}{\partial r}(r^2\frac{\partial D}{\partial r}) - \lambda_D D + \Gamma(D_B - D)$$
$$-\left\{u_T K_T(1-e^{-\sigma_T D})T + -U_N K_N(1-e^{-\sigma_N D})N - U_C K_C(1-e^{-\sigma_C D})C\right\} \tag{2.20}$$

$$\frac{\partial S}{\partial t} = \frac{dS}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial S}{\partial r}\right) - \lambda_S S + TH(R(t)-r) \tag{2.21}$$

$$\frac{\partial N}{\partial t}+\left\{u\frac{\partial N}{\partial t}+\frac{N}{r^2}\frac{\partial}{\partial r}\left(r^2u\right)\right\}+a_N\left\{\frac{\partial S}{\partial r}\frac{\partial N}{\partial r}+\frac{N}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial S}{\partial r}\right)\right\}$$

$$=\frac{\partial_N}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial N}{\partial r}\right)-\lambda_N N-i_N NT-K_N(1-e^{-\sigma_N D})N \qquad (2.22)$$

$$\frac{\partial C}{\partial t}+\left\{u\frac{\partial N}{\partial t}+\frac{N}{r^2}\frac{\partial}{\partial r}\left(r^2u\right)\right\}+a_C\left\{\frac{\partial S}{\partial r}\frac{\partial C}{\partial r}+\frac{C}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial S}{\partial r}\right)\right\}$$

$$=\frac{\partial_C}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right)-\lambda_C C-i_C CT-K_C(1-e^{-\sigma_C D})C \qquad (2.23)$$

with

$$\frac{dR}{dt}=U(R(t),t)$$

These are the modeled equations for the drug-cells interaction on the tumor described here as inhibited growth.. The evolution of the tumor boundary is as specified above.

## 2.1 SOLUTIONS OF THE MODEL

We now consider analytic solutions to our model. We seek solutions to our model equation for the delay period using additional sets of assumptions.

## 2.2 DRUG-INHIBITED TUMOR GROWTH

We now suppose that the intra tumor drug concentration D is constant, so that equation (2.19) becomes

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2u)=1-k_T(1-e^{-\sigma_T D}) \qquad (2.2.1)$$

Integrating (2.1.3), this will yield

$$\int_0^r\left[1-k_T\left(1-e^{-r_T D}\right)\right]ds=\left[1-k_T\left(1-e^{-r_T D}\right)\right]r$$

From

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2u)$$

Using changing of variables, we have

$$\int\frac{1}{s^2}\frac{\partial}{\partial s}(s^2u)ds=\int ds$$

$$\frac{1}{s^2}\cdot S^2u\Big|_0^r-\int S^2u\cdot\frac{2S}{S^3}ds \quad \text{(Integration by paths) we have}$$

$$=u-2\int_0^r uds=u+2u=3u$$

Therefore, we hold that

$$\int\frac{1}{s^2}\frac{\partial}{\partial s}(s^2u)ds=3u$$

Also,

$$\int_0^r\left[1-k_T\left(1-e^{-r_T D}\right)\right]ds=\left[1-k_T\left(1-e^{-r_T D}\right)\right]s\Big|_0^r$$

$$=\left[1-k_T\left(1-e^{-r_T D}\right)\right]r-(\ )*0$$

$$3u=\left[1-k_T\left(1-e^{-r_T D}\right)\right]r$$

$$u = \frac{1 - k_T\left(1 - e^{-r_T D}\right)}{3} r$$

$$u(r) = \left(1 - k_T\left(1 - e^{-\sigma_T D}\right)\right)\frac{r}{3} \quad - \quad - \quad - \quad - \quad - \quad (2.2.2)$$

Then applying (2.17) we now have

$$\frac{dR}{dt} u\left(R(t), t\right) = \frac{1 - \left(k_T\left(1 - e^{-\sigma_T D}\right)\right.}{3} R(t), \quad - \quad - \quad (2.2.3)$$

$$R(t) = R_o e^{(1 - k_T(1 - e^{-\sigma_T D}))t} \quad - \quad - \quad - \quad - \quad (2.2.4)$$

**ANALYTIC SOLUTION OF LOCAL DRUG EQUATION**

We make similar assumption regarding the chemotherapy drug to obtain analytic solution. We assume that drug diffuses much faster than the tumor grows. We again consider the case in which there is no local immune presence, so that $N = C = 0$

This yield the normalized equation

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial D}{\partial r}\right) - \frac{1}{d_D}\left(\lambda_D D - \Gamma\left(D_B - D\right) + U_T k_T\left(1 - e^{-\sigma_T D}\right)T\right) = 0 \quad (2.2.15)$$

subject to the initial boundary condition $D_r(0) = 0$ and $DR(t) = D_N(t)$

If we assume low drug concentrations, then $1 - e^{-\sigma_T D} = \sigma_T D$ and we have

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial D}{\partial r}\right) - \frac{1}{d_D}\left(\lambda_D + \Gamma + U_T k_T \sigma_T T\right)D = -\frac{1}{d_D}\Gamma D_B$$

Let

$$\xi_D^2 = \frac{\lambda_D + \Gamma + U_T k_T \sigma_T T}{d_D} \quad (2.2.16)$$

Then the non-homogeneous PDE above becomes

$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial D}{\partial r}\right) - \xi_D^2 D = -\frac{\Gamma}{d_D} D_B(t)$$

A particular solution to the equation is

$$D = \frac{\Gamma}{d_D \xi_D^2} D_B(t)$$

So that the homogeneous equation is

$$F'' - \xi_D^2 F = 0$$

$$m^2 - \xi_D^2 = 0$$

$$m^2 = \xi_D^2$$

$$D(r,t) = a(t)Sinh\xi_D + b(t)Cosh\xi_D$$

The general solution will be

$$D(r,t) = a(t)Sinh\xi_D + b(t)Cosh\xi_D + \frac{\Gamma}{d_D \xi_D^2} D_{B(t)}$$

where $a(t)$ and $b(t)$ $m = \pm\xi_D = a(t)e^{a(t)\xi_D} + b(t)e^{-\xi_D}$ are constants or

$$D(r,t) = C_1 e^{\xi_D t} + C_2 e^{-\xi_D t} + \frac{\Gamma}{d_D \xi_D^2} D_{B(t)}$$

At $D(r,t) = 0$ we require that $b(t) = 0$

or $C_2 = 0$, $r = R(t)$

$$D(R(t),t) = a(t)Sinh\xi_D + \frac{\Gamma}{d_D\xi_D^2}D_B$$

or $D(R(t),t) = C_1 e^{\xi_D t} + \frac{\Gamma}{d_D\xi_D^2}D_{B(t)}$

$D(r,t) = a(t)Sinh\xi D^r + b(t)Cosh\xi D^r + \frac{\Gamma}{d_D\xi_D^2}D_B$ At $Dr(0) = 0$ requires that $b(t) = 0$

At $r = R(t)$

$$D(R(t),t) = a(t)\frac{Sinh\xi DR}{R} + \frac{\Gamma}{d_D\xi_D^2}D_B(t)$$

**Theorem:**

If $f : Q^+ \to R$ is continuous and $U : Q^+ \to R$ is a solution of the following non-homogenous initial/boundary value problem

$$\begin{cases} U_t(x,t) - U_{xx}(x,t) = f(x,t) \\ U(x,0) = 0, x \in [0,1] \\ U(0,t) = U(1,t) = 0 \end{cases}$$

for every $t \in [0,1]$ where

$Q^+ = \{(x,t) \in IR^2 : 0 < x < 1, 0 < t < \infty\} =$ closure of $Q^+$

Now for every $P \in [0,\infty)$

Let $H_t - H_{xx} = 0 \qquad (x,t) \in [0,1]X[P,\infty]$

$H(x,t,P) = f(x,P) \qquad x \in [0,1)$

$H(0,t,P) = H(1,t,P) = 0 \qquad t \in [P,\infty)$

Then $U$ and $H$ satisfy

$$U(x,t) = \int_0^t H(x,t,P)dp$$

We shall adopt the techniques in the Duhamel principle to solve (2.23) after some modification. Hence,

$$\frac{\partial C}{\partial t} + a_C\nabla.(C\nabla S) = d_c\nabla^2 C - \lambda_C C - i_c l_{cT} - L_{CD}(C,D)$$

The parameters $a_c, N_c, \lambda_c, i_c$ and $l_{cD}$ are as defined previously.

$$\frac{\partial C}{\partial t} + a_C\nabla.(C\nabla S) = d_c\nabla^2 C - \lambda_C C - i_c l_{cT} - L_{CD}(C,D) \qquad (2.3.1)$$

$$\frac{\partial C}{\partial t} - d_c\nabla^2 C = -\lambda_C C - i_c l_{cT} - L_{CD} - a_C\nabla.(C\nabla S)$$

Set $\quad -\lambda_C C - i_c l_{cT} - L_{CD} - a_C\nabla.(C\nabla S) = f(x,t)$

$$\frac{\partial C}{\partial t} - d_c\nabla^2 C = f(x,t) \qquad (2.3.2)$$

as stated in Duhamel principle

$$\frac{\partial C}{\partial t} - 2d_c\frac{\partial^2 C}{\partial x^2} = f(x,t)$$

We adopt the same boundary conditions in Duhamel's principle with

$u(x,t) = c(x,t)$

$$C(x,t) = \int_0^t H(x,t,P)dp$$

We have

$$H_t - 2d_N H_{xx} = 0 \qquad (x,t) \in [0,1]\times[p,\infty] \tag{2.3.3}$$

So let $H(x,t,p) = X(x)T(t)Y(p)$

$$H_t = X\dot{T}Y$$

$$H_{xx} = X''YT$$

Substituting in (2.3.3)

$$X\dot{T}Y = 2dX''TY$$

$$\frac{\dot{T}}{T} - 2d_c\frac{X''}{X} = 0$$

Let $\frac{\dot{T}}{T} - 2d_c\frac{X''}{X} = k^2$

$$\frac{\dot{T}}{T} = k^2 \tag{2.3.4}$$

$$InT = k^2 + \lambda_1$$

$$T = e^{k^2+\lambda_1}$$

and $\qquad 2d_c\frac{X''}{X} = m^2$

$$\frac{X''}{X} = \frac{1}{2d_c}m^2$$

$$X'' = \frac{1}{2d_c}m^2X$$

$$\frac{\dot{T}}{T} - 2d_c\frac{X''}{X} = 0$$

$$\frac{1}{2d_c}\frac{\dot{T}}{T} - \frac{X''}{X} = 0$$

$$\frac{1}{2d_c}\frac{\dot{T}}{T} - \frac{X''}{X} = m^2$$

Therefore, $\frac{1}{2d_c}\frac{\dot{T}}{T} = -m^2$ (2.3.4)

and $\frac{X''}{X} = -m^2$ (2.3.5)

From (2.3.4) $\qquad \frac{\dot{T}}{T} = 2d_cm^2$

$$InT = 2d_cm^2t + \lambda_1$$

$$T = e^{2d_cm^2t+\lambda_1} \qquad \text{let } e^{\lambda_1} = \beta$$

$$T(x,t) = \beta e^{2d_cm^2t_1} \tag{2.3.6}$$

$$X'' + m^2X = 0$$

The auxiliary equation now will become

$$k^2 + m^2 = 0$$
$$k = \pm m$$
$$X(x) = A_1 e^{-mx} + A_2 e^{mx}$$
$$H(x,t,p) = X(x)T(t)Y(p) = \left(A_1 e^{-mx} + A_2 e^{mx}\right)\beta e^{2d_C m^2 t} Y(p)$$
$$\Rightarrow H(x,t,p) = \beta e^{2d_C m^2 t}\left(A_1 e^{-kx} + A_2 e^{kx}\right)\varphi dp$$
$$= \beta e^{2d_C m^2 t}\left(A_1 e^{-kx} + A_2 e^{kx}\right)\varphi \int_0^t dp$$
$$= \beta e^{2d_C m^2 t}\left(A_1 e^{-kx} + A_2 e^{kx}\right)\varphi(t)$$
$$H(x,t,p) = \beta e^{2d_C m^2 t}\left(A_1 e^{-kx} + A_2 e^{kx}\right)\varphi t \qquad (2.3.7)$$

## 3.0 ANALYSIS AND DISCUSSION

In this analysis, we used collected data to test for the validity of the models most especially the tumor growth in the presence and non-presence of chemotherapy. In the case of the non-usage of chemotherapy to control the growth of the tumour cells, we called it the un-inhibited tumour growth and the other we call the inhibited tumour growth. We shall carry out our analysis in these lines to study the interaction of the chemotherapy and immunology with the cancer cells. The necessary amounts of drugs which can manage the growth rate of tumor so that it can be considered to be at dormant stage so as not to kill the host for a long period is also studied.

### 3.1 CHEMOTHERAPY TREATMENT

Tumor left untreated would grow to a dangerous level. In equations (2.1.2) – (2.1.6), we modeled some set of equations with pulse chemotherapy administration into the body after the tumor is large enough to be detected. In these models, we consider chemotherapy as the only external treatment and expected to control the tumour growth. We examined the tumor response to pulse chemotherapy by incrementing pulses.

### 3.3 Inhibited Tumour Growth

Here we consider the treatment with chemotherapy to see if the cancer cell proliferation can be controlled or eradicated. In Fig. 4, we can see that with this treatment, the tumour cells boundary reduces over varied levels of drug administration. However, using a single dose of drug over time shows that the cell boundary increases after sometime, (Fig. 2 & 3). This shows that the administration of the chemotherapy can control the proliferation of the cancer cells in a patient if it is administered at varied levels of the drug but we must be careful of the level of the drug to be used.

Furthermore, Fig. 5 shows that as the tumour boundary increases, we require higher levels of the drug to control the cell proliferation. This suggests and confirms the requirement that patients should come forward for treatment as quickly as possible to reduce the level of drug treatment.

### 3.4 CONCLUSION

It is our hope that, these models with their analytic solutions will give better understanding of the growth pattern of cancer cells and the control procedures for the clinicians and medical Doctors treating the cancer cell proliferations in a patient.

We equally saw that drug doses cannot be administered arbitrarily. Individuals has to be tested to ascertain the health level before drug is administered.

### 3.5 RECOMMENDATION

We recommend these models to those in the medical field to enhance their efficient control of cancer in their patients. A lot of progresses are being made in that field, but we still recommend that, these models should be considered to prevent frequent loss of life resulting from treatment of tumour/cancer of any kind due to wrong levels of drug administered.

We are aware that since most of the modeled equations are non-linear, one of the best methods of solution would have been the Numerical approach. Yet, we used analytical method to demonstrate those simplified assumptions valid for cancerous tumours, like the ineffectiveness of the Natural Killer, $CD8^+$ and the cytotoxic lymphocytes, in controlling cancerous cells. Therefore, one can attempt studying these same models using other methods different from analytical approach.

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**Appendix.**

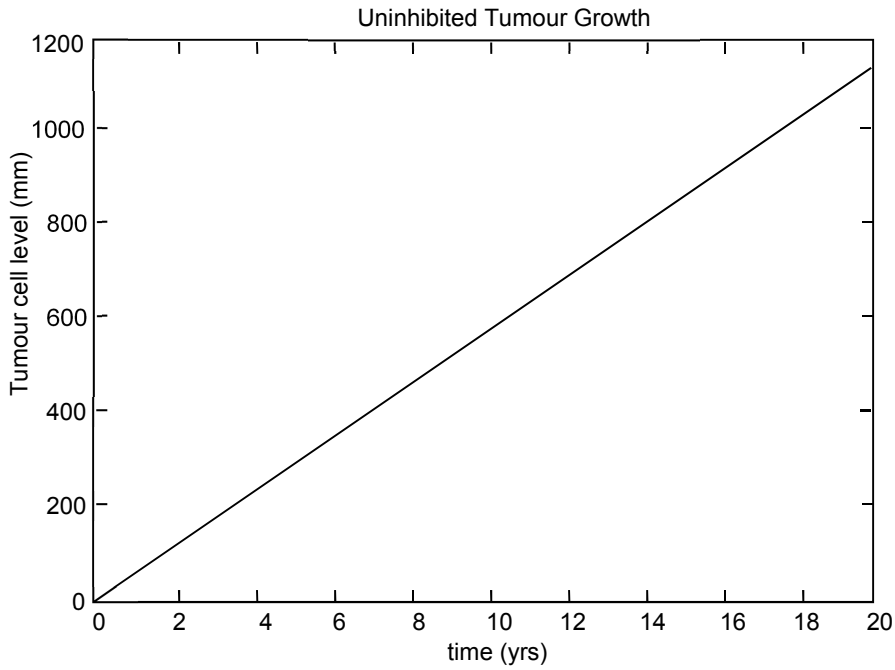


**Fig. 1**

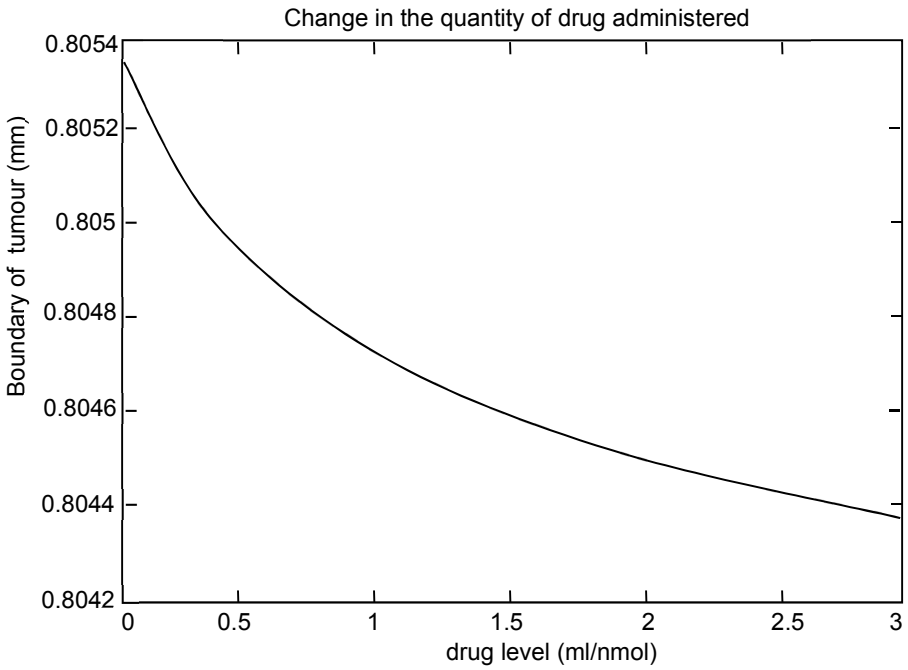


**Fig. 2**

 

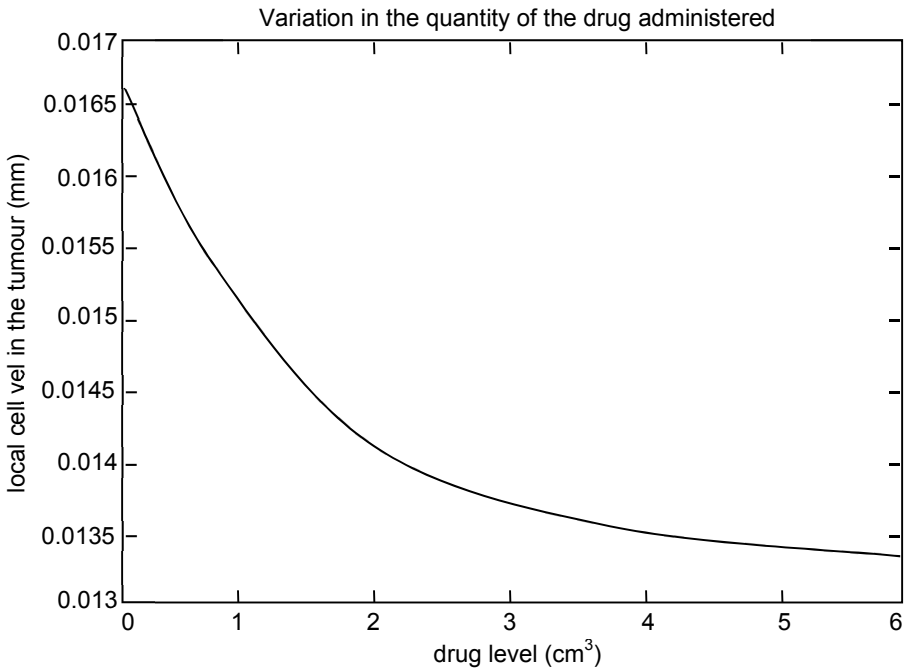
Variation in the quantity of the drug administered
local cell vel in the tumour (mm)
0.017
0.0165
0.016
0.0155
0.015
0.0145
0.014
0.0135
0.013
0
1
2
3
4
5
6
drug level (cm3)

**Fig. 3**

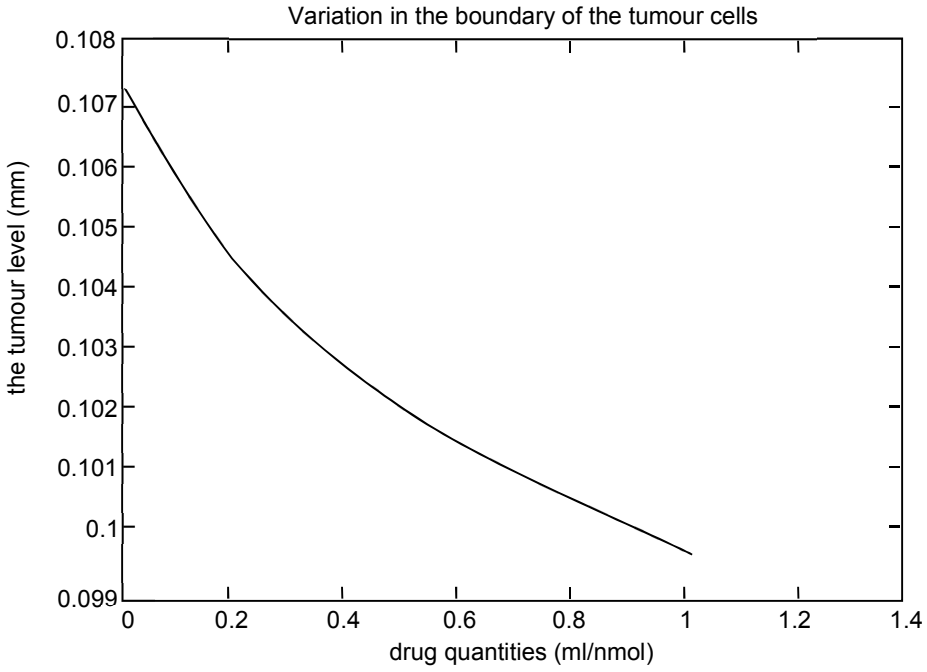
Variation in the boundary of the tumour cells
the tumour level (mm)
0.108
0.107
0.106
0.105
0.104
0.103
0.102
0.101
0.1
0.099
0
0.2
0.4
0.6
0.8
1
1.2
1.4
drug quantities (ml/nmol)

**Fig. 4**

 

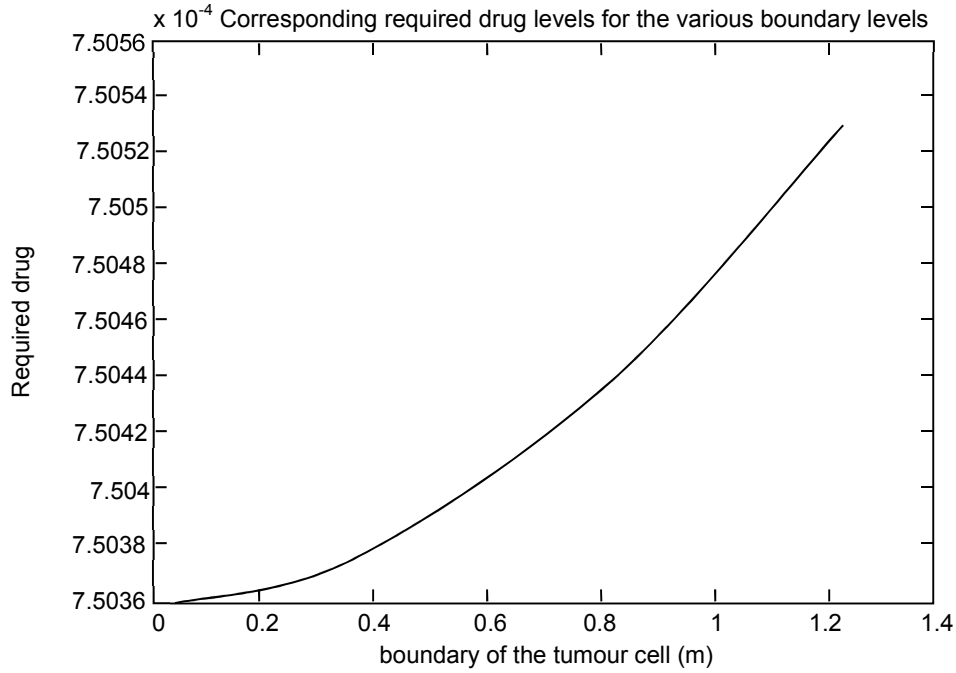
x 10-4 Corresponding required drug levels for the various boundary levels
Required drug
7.5056
7.5054
7.5052
7.505
7.5048
7.5046
7.5044
7.5042
7.504
7.5038
7.5036
0
0.2
0.4
0.6
0.8
1
1.2
1.4
boundary of the tumour cell (m)

**Fig. 5**

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